REPLY TO OFFICE ACTION UNDER 37 C.F.R. § 1.111

In response to the non-final Office Action dated June 30, 2000, Applicants submit the following remarks.

Remarks

Claims 18-29 are pending and being examined.

The Examiner noted at page 2 of Paper No. 4, that reference to the prior application is missing from the specification. However, Applicants, in their Preliminary Amendment of September 24, 1999, amended the specification to include reference to application 08/737,953, filed November 27, 1996. Applicants respectfully request clarification if there are additional statements required.

I. The Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 21, 22, and 24-29 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to describe the subject matter in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully disagree.

The Examiner asserts that the specification "fails to describe all or part of calpastatin and any other calpain inhibitors and its function in regulating cellular levels of p53." (*See* page 3 of Paper No. 4.) First, one skilled in the art was familiar with calpains, as the specification makes clear at pages 4 and 5. In addition, one skilled in the art was familiar with inhibiting the calpains by using both calcium chelators and proteins like calpastatin (*see* page 5, lines 16-24).

Applicants respectfully do not understand how one skilled in the art could possibly doubt that the inventors were in possession of these inhibitors in light of at least these parts of the specification and what was known in the art. Furthermore, SEQ ID NO. 1 sets forth the amino acid and nucleotide structure of human calpastatin. What other indication of possession could be needed? In addition, one skilled in the art is clearly able to take a nucleotide sequence and produce fragments of it or produce fragments of its encoded amino acid sequence. Applicants request clarification if this assertion is to be maintained.

With respect to calpain inhibitors' function in regulating cellular levels of p53, applicants state in numerous places in the specification that p53 proteins are substrates for calcium-dependent proteases, like the calpains (*see* page 3, lines 26-28, for example). From this one statement alone anyone of skill in the art would understand that applicants were in possession of the knowledge that calpain inhibitors effect p53 activity. And, since one skilled in the art clearly knew of methods to test the presence of degraded p53 (*see* page 3, lines 22-25), one could easily test if any calpain inhibitors would prevent the degradation of p53. Thus, one skilled in the art would not doubt that applicants invented and described the aspect of these claims that involves regulating p53. In fact, later publications confirm that applicants' statements are true and leave no room for doubt (*see* published PCT document WO 00/21575, PTO Form 1449 provided, at page 18, lines 12-17).

With respect to vectors, applicants clearly describe that the nucleic acids can be part of vectors. "Preferably, the sequence used within the framework of the invention form part of a vector." (*See* specification at page 9, lines 9-10.) On top of the other more detailed descriptions of vectors that can be used found in the specification, one skilled in the art would not doubt that applicants had in their possession nucleic acid sequences encoding calpain inhibitors that can be

inserted into a vector. The fact that one skilled in the art recognizes that this can be done and understands what these words mean can be seen from the WO 00/21575 document. Furthermore, the original claims describe the subject matter now claimed in a manner sufficient for one skilled in the art to understand that the inventors did indeed invent and possess the claims invention.

Applicants respectfully request reconsideration and withdrawal of this rejection in light of the evidence provided and arguments made.

B. Enablement

Claims 18-29 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly enables only vectors comprising a full length calpastatin that are used in direct intra-tumoral administration. Applicants respectfully disagree.

The Examiner sites many general articles and concludes that gene therapy is not effective and unpredictable. However, it is clear that applicants affirmatively state in their application that the methods and viral vectors of the invention are capable of generating, *in vivo*, an effect on the regulation of p53 levels in a cell (*see* page 4, lines 9-20, and pages 9, lines 9-10 and 19-28). In light of these statements and the examples and data demonstrating the effect on p53 levels in cells, applicants have asserted and shown that the claims are enabled. Applicants' assertions are presumptively correct. As a result, it is the Examiner's burden to provide evidence that one of skill in the art would consider contradictory or inconsistent. *In re Marzocchi,* 169 U.S.P.Q. 367, 370 (C.C.P.A. 1973) ("It is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is *inconsistent* with the contested statement.")

Applicants also note that the standard for the how to use aspect of § 112, first paragraph, for pharmaceutical inventions falls well short of a demonstration of the therapeutic effectiveness that the FDA requires. *In re Brana*, 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995). Any desirable property, even if further research and development may be required, suffices.

In this case, one of skill in the art is clearly aware of the importance and experience the field has with p53 proteins. This knowledge together with applicants' disclosure that calpain inhibitors can effect the p53 level in a cell would clearly allow one of skill in the art to make and use vectors and methods as claimed.

Applicants enclose a recent article discussing how modulating p53 can be done even in human *in vivo* trials (Anderson, Nature Medicine 2000, Form PTO-1449 provided). Since that article also uses a viral vector, there does not seem to be a reason for the PTO to express concerns over effectiveness even if they followed the appropriate standard. Furthermore, the article states that it is "regulatory concerns" and not the ability of one to make and use gene therapy inventions that is the real issue in effectiveness. As shown below, those FDA "regulatory concerns" are not the province of the Patent Office.

Applicants respectfully restate the legal standard appropriate here. An applicant for patent is not required to provide therapeutic or clinical data in order to obtain a patent. As stated in *In re Brana*, the Patent Office must not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana,* 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). Quoting the C.C.P.A. from *In re Krimmel*, the court in *Brana* stated:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to

> the art, even though it may eventually appear that the compound is without value in the treatment of humans.

The court continued:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which the invention in this field becomes useful is well before it is ready to be administered to human. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
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> *In re Brana,* 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995).

At this point it would be inappropriate to deny patent protection to applicants' invention merely because of a lack of human clinical trial data that correlates with the successful *in vitro* data. Denial on that basis would prematurely curtail research and development into a promising therapeutic approach to cancer, which the courts recognize as a "crucial" area of research.

In this case, an advance in the approach for treating cancer by the well known effect of regulating p53 levels in cancer suffices for patenability. The Examiner does not appear to question that the specification provides an advantageous or desirable approach in the research and development of cancer therapies. Accordingly, as previously held in *Brana*, the PTO should not require additional data here.

Paper No. 4 also mentions a number of documents that apparently address the unpredictability of gene therapy treatments on a therapeutic level. These documents, and the discussion of them, do not address the appropriate standard noted above. Furthermore, even if an invention operates inefficiently, transiently, or in a manner that some consider as needing improvement, it can still satisfy the legal standards of patentability. All that is needed is some desirable property. *In re Brana,* 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). The Examiner has not concluded that the invention as claimed completely lacks a desirable property. Therefore, the discussion of how others may feel on efficient, FDA approvable gene therapies is irrelevant.

Applicants submit that in light of the arguments and evidence provided a *prima facie* case of lack of enablement has not been made. Accordingly, applicants request the withdrawal of this rejection.

II. The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 18-28 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. Applicants respectfully traverse this rejection.

The Examiner asserts that "the activity of calpain" is vague and indefinite. However, as noted above, one of skill in the art was familiar with calpain, its activity, and specific inhibitors of that activity. Therefore, one of skill in the art would have no trouble understanding what the phrase "the activity of calpain" means.

In addition, the term "regulating" that the Examiner notes at page 12 of Paper No. 4 is also well known to those of skill in the art. The data in Figure 1 specifically shows the regulation of p53 and how one can detect it using methods well known in the art (*see* also page 17, lines 18-26 of the specification). Nothing in Paper No. 4 indicates why one of skill in the art would not understand the claims as they are currently written.

Applicants request reconsideration and withdrawal of this rejection.

III. The Rejection Under 35 U.S.C. § 102

Claim 29 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Asada et al. Applicants respectfully disagree.

The Examiner asserts, at page 12 of Paper No. 4, that Asada teaches a cDNA of human calpastatin. However, nothing in the rejection indicates that every element of claim 29 has been

discloses, as required for anticipation. Here, there is no indication that a composition from Asada could inhibit a calpain. The Examiner points to no such teaching. Furthermore, the Examiner points to no teaching of a composition formulated for intra-tumoral administration. Without these specific teachings, Asada cannot anticipate claim 29.

Applicants respectfully request the withdrawal of this rejection.

Claims 26-29 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Nixon et al. Applicants respectfully disagree.

Nowhere does Nixon teach or even suggest a nucleic acid encoding a protein or polypeptide that is an inhibitor of the activity of calpain. Nixon analyzes proteins derived from cells but does not disclose a calpastin cDNA as the Examiner asserts at page 13 of Paper No. 4. Without the nucleic acid encoding calpastatin, Nixon cannot anticipate any of the claims.

Applicants respectfully request reconsideration and withdrawal.

IV. Conclusion

Applicants believe that this application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with applicant's representative, in person or by telephone, we would welcome the opportunity to do so.

Applicants have provided for a three-month extension above. No additional extension of time fees, requests for extension of time, petitions, or additional claim fees are believed to be necessary to enter and consider this paper. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request

any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account # 50-1640 for any fees. If there is any variance between the fee submitted and any fee required, including the extension of time fee and fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1640.

Respectfully submitted,
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